REMARKS

Claims 1, 5, 41, 46, 63 and 64 are pending in the instant application. All claims remain rejected by the Examiner for the supposed lack of utility and enablement. Applicants traverse these rejections for the reasons stated below and make arguments in further response to the Final Office Action.

No art was cited against the instant application.

Examiner's Position in the Advisory Action

The Examiner in the Advisory Action stated that Applicants' previous request for reconsideration was considered but did not place the application in condition for allowance because the "asserted use of 'promoting growth of cells in the lining of the GI tract in order to treat intestinal inflammation and ulcers' is not specifically recited in the specification as filed because it is but one in a list of unrelated uses." Applicants traverse.

Examiner's Position in the Final Office Action

In the pending Office Action, the Examiner made the following rejections:

(1) 35 U.S.C. §101 - Claims 1, 5, 41, 46 and 63-64 were finally rejected as not supported by a specific, substantial, or credible utility.

(2) 35 U.S.C. §112, first paragraph - Claims 1, 5, 41, 46 and 63-64 were finally rejected for failing to adequately enable one skilled in the art to use the claimed invention, given the above rejection under 35 U.S.C. §101.

Applicants traverse each of these rejections as applied to the claims as pending. A discussion of the patentability of the claims presented herein is discussed below.

35 U.S.C. § 101 utility requirement is met.

Claims 1, 5, 41, 46 and 63-64 have been rejected in the parent case as lacking utility and as being non-enabled. In the Advisory Action, the Examiner contends that because multiple utilities are recited in the specification, that no "specific" utility has been recited. In the Final Office Action on pages 3-4, the Examiner set forth multiple reasons for rejecting Applicants' previous showing of specific examples of utility.

The arguments below establish why the claims presented herein are patentable.

The record is clear that the specification makes a specific assertion of utility for the claimed invention – in this case the polypeptide comprising the novel fibroblast growth factor-20 ("FGF-20") of SEQ ID NO:2. The proteins of this invention may be used to stimulate cell growth, including especially growth of fibroblasts and epithelial cells in the linings of the gastrointestinal tract. The specification expressly states this as a specific, substantial credible utility. See, *e.g.*, the following sections in the disclosure:

"The proteins of the invention may be used to stimulate cell growth and cell proliferation in conditions in which such growth would be favorable. An example would be to counteract toxic side effects of chemotherapeutic agents on, for example, hematopoiesis and platelet formation, linings of the gastrointestinal tract, and hair follicles." *See*, p. 77, lines 26-29.

"Uses and Methods of the Invention" section, extending from p. 67 through p. 90.

The "Diagnostic Assays" subsection (pp. 76-79) details stimulation of epithelial cells, glial cells, and cells found in the lining of the gastrointestinal tract. See, *e.g.*, p. 76, line 29, through p. 77, line 9; p. 77, lines 26 – 31. Such stimulation can be used to heal wounds and ulcers. See, *e.g.*, p. 76, lines 29-30.

Applicants have submitted unequivocal evidence of record that confirms that the proteins claimed in the invention have precisely this activity. In fact, applicants previously made of record applicants' published work demonstrating that administration of FGF-20 protein in fact "enhances the growth of intestinal fibroblasts." See, Jeffers *et al.*, Gastroenterology, 123, pp. 1151-62 (2002) (citing Abstract), filed on February 6, 2003.

In addition, applicants submit herewith, in Appendix A, a Press Release announcing the FDA approval of CuraGen's (the assignee of this application) Investigational New Drug application to initiate human clinical trials using FGF-20 to treat oral mucositis – oral mucositis is a side effect of chemotherapy and radiotherapy that results in degradation of mucosal tissue that can range from redness and irritation to severe ulcerations of the mouth and throat. In this trial, FGF-20 is being tested for its ability to stimulate cell proliferation (specifically proliferation of fibroblasts and epithelial cells) and to counteract toxic side effects of chemotherapeutic and

radiotherapeutic agents in the throat and mouth (*i.e.*, linings of the gastrointestinal tract), precisely as recited in the specification. This is all that is required to prove an overabundance of utility.

For the record, Applicants note that utility is also supported by the structural similarity of this FGF-20 with other known members of the FGF family and specifically contains a conserved family domain and hydrophobic transport domain. In addition, the FGF-20 polypeptide claimed here has a biological activity similar to a structurally related fibroblast growth factor-9 (FGF-9) compound already known and tested in the art for activation/proliferation of glial cells and fibroblasts. *See*, specification at least at, *e.g.*, pp. 76-77, & FIGS. 4-5. Other known FGFs have been demonstrated to be useful in the stimulation of wound healing; see, *e.g.*, U.S. Patent No. 5,804,213. In addition, case law holds as valid a utility for claimed compounds based on structural features similar to the facts in the instant application, *e.g.*, *In re Jolles*, 628 F.2d 1322 (C.C.P.A. 1980)(finding utility for claimed compounds having close structural relationship to other compounds known to be useful in cancer therapy); *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995)(stating that although it may be true that minor changes in chemical compounds can radically alter their effects, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility). Thus, the particular utility asserted here, namely diagnosing and treating cell proliferation associated disorders such as wound healing associated with oral mucositosis for FGF-20, is fully supported and consistent with generally accepted scientific principles and with current case law.

The Examiner in the Advisory Action asserted that applicants response filed February 6, 2003, did not place the application in condition for allowance because the "asserted use of 'promoting growth of cells in the lining of the GI tract in order to treat intestinal inflammation and ulcers' is not specifically recited in the specification as filed because *it is but one in a list of unrelated uses*" (emphasis added). The fact that multiple utilities are recited in the specification does not mean that there is a lack of a specific, substantial and credible utility. As the MPEP makes clear, "[i]t is common and sensible for an applicant to identify several specific utilities for an invention." See MPEP § 2107.01. The case law is also clear. In re Gottlieb 328 F.2d 1016 (CCPA), is particularly relevant. In Gottlieb, multiple utilities were disclosed. The Court held that one specific utility was sufficient to meet the utility requirement (328 F.2d at 1018). That is all that is required here also. *See also* In re Brana 51 F.3d 1560 (Fed.Cir. 1995).

Applicants assert that the polypeptide comprising SEQ ID NO:2 does have a credible utility, namely promoting growth of cells in the lining of the gastrointestinal tract in order to treat intestinal inflammation and ulcers. This demonstrated utility was discussed during a telephone conference with the Examiner on January 9, 2003. This activity was disclosed in the specification as originally filed and has now been published in Jeffers, *et al*, 2002 *Gastroenterology* 123: 1151-1162 (filed in the February 6, 2003, Response as Appendix A). As discussed during the Examiner phone conference, this utility of treating ulcers and cells lining the gastrointestinal tract was disclosed in the specification in various locations, including at least the following:

> "The invention includes a method of promoting growth of cells in a subject...In some embodiments, the cells whose growth is to be promoted may be ... cells in the lining of the gastrointestinal tract." page 5, lines 15-21.
>
> "FGF-CX can also be used to stimulate fibroblasts (for accelerating healing of ... ulcers)" page 77, lines 29-30.
>
> "The proteins of the invention may be used to stimulate cell growth and cell proliferation in conditions in which such growth would be favorable. An example would be [in] ... linings of the gastrointestinal tract." page 77, lines 26-29.

As illustrated above, the specification discloses utility of the proteins of this invention for treating ulcers and cells lining the gastrointestinal tract. As illustrated in the previously provided Jeffers article, the proteins of this invention have a demonstrated therapeutic activity of treating intestinal inflammation in both animal *in vivo* studies and human *in vitro* studies. In a murine-colitis model, it was shown that prophylactic administration of FGF-20 (corresponding to SEQ ID NO:2 of the pending claims) significantly reduced the severity and extent of mucosal damage. In a rat small bowel ulceration/inflammation model, administration of FGF-20 was shown to reduce small intestinal weight gain, necrosis, inflammation, and weight loss. And human *in vitro* studies demonstrated that FGF-20 stimulated cell growth and restitution in human intestinal fibroblasts. Accordingly, FGF-20 (SEQ ID NO:2) has been shown to have a specific, substantial, and credible utility of treating intestinal disorders. This utility was specifically disclosed in the specification as originally filed. Applicants request, therefore, that all pending rejections be withdrawn, since utility has been demonstrated herein.

35 U.S.C. § 112, first paragraph, rejection is overcome.

Claims 1, 5, 41, 46 and 63-64 were finally rejected for failing to adequately enable one skilled in the art to use the claimed invention, given the above rejection under 35 U.S.C. §101. Applicants traverse.

The Examiner has implicated a "how to use" utility-based § 112, first paragraph, rejection. This cannot stand. To uphold a utility-based § 112, first paragraph, non-enablement rejection, a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result." Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555 (Fed. Cir. 1992), as discussed in the Legal Analysis accompanying the Utility Guidelines (M.P.E.P. § 2107). The only instances in which the Federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention *could and did not work* as the inventor claimed it did." M.P.E.P. § 2107 (emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.01. That is simply not the case here -- as is plain from Jeffers paper, and the FDA's approval of the IND.

The rejection should be withdrawn.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance, and request an action be issued to this effect. The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 15966-557 CIP (Cura-57 CIP). If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Dated: April 14, 2003

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Appendix A:

Press Release:
CuraGen Receives FDA Approval to Initiate Clinical Trials

<http://www.curagen.com/ir/FPR.htm>

Investor Relations

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CuraGen Corporation (ticker: CRGN, exchange: NASDAQ) News Release - 4-Mar-2003

CuraGen Receives FDA Approval to Initiate Clinical Trials

Potential Oral Mucositis Treatment Marks Successful Transition into Drug Development

NEW HAVEN, Conn., Mar 4, 2003 /PRNewswire-FirstCall via COMTEX/ --CuraGen Corporation (Nasdaq: CRGN), a genomics-based pharmaceutical company, today announced that the U.S. Food and Drug Administration (FDA) has approved its Investigational New Drug (IND) application to initiate clinical trials for CG53135, a potential protein therapeutic being investigated as a treatment for oral mucositis. Oral mucositis is a side effect of chemotherapy and radiotherapy that results in the degradation of mucosal tissue that can range from redness and irritation to severe ulcerations of the mouth and throat. CuraGen now plans to proceed with a multi-center Phase I clinical trial to evaluate safety and pharmacokinetics in patients with cancer who are at risk for mucositis following chemotherapy.

Mucositis is a debilitating complication of cancer chemotherapy or radiotherapy that affects the mucosal tissue, which acts as a protective lining within the digestive track, including the mouth and throat. Symptoms range from pain and discomfort to severe ulcerations that limit a patient's ability to ingest nutrients. Mucositis can result in a suppressed immune system that can reduce a patient's ability to tolerate further cancer therapy. Delayed treatment can lessen the effectiveness of the chemotherapy or radiotherapy, adversely impacting the value of the patient's overall treatment regimen.

"CG53135 is a novel protein discovered through the application of CuraGen's functional genomic technologies. In preclinical studies, this potential protein therapeutic reduced tissue inflammation and degeneration, and minimized the severity and extent of mucosal tissue damage. Mucositis is a significant unmet medical need, and we are pleased to have the opportunity to advance this promising molecule into human clinical trials," stated Timothy M. Shannon, M.D., Senior Vice President of R&D and Chief Medical Officer of CuraGen Corporation.

"Through the filing of this IND, CuraGen has become one of the first genomics companies to successfully transition from a target discovery company into a genomics-based pharmaceutical company. This molecule represents the first of many promising candidates that we believe will emerge from our portfolio of discovery and preclinical stage projects. We are pleased with the progress of this potential therapeutic and look forward to additional future successes," stated Jonathan M. Rothberg, Ph.D., Founder, Chairman, and CEO of CuraGen Corporation.

About CuraGen

CuraGen Corporation (NASDAQ: CRGN) is a genomics-based pharmaceutical company. CuraGen's integrated, functional genomic technologies and Internet-based bioinformatic systems are designed to generate comprehensive information about genes, human genetic variations, gene expression, protein interactions, protein pathways, and potential drugs that affect these pathways. The Company is applying its industrialized genomic technologies, informatics, and validation technologies to develop protein, antibody, and small molecule therapeutics to treat obesity and diabetes, cancer, inflammatory diseases, and central nervous system (CNS) disorders. CuraGen is headquartered in New Haven, CT and additional information is available at www.curagen.com.

This press release may contain forward-looking statements including statements about CG53135's demonstrated ability to reduce tissue inflammation and degeneration, and minimize the severity and extent of mucosal tissue damage in preclinical studies, as well as representing the first of many promising candidates that we believe will emerge from our portfolio of discovery and preclinical stage projects. Such statements are based on management's current expectations and are subject to a number of factors and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. CuraGen cautions investors that there can be no assurance that actual results or business conditions will not differ materially from those projected or suggested in such forward-looking statements as a result of various factors, including, but not limited to, the following: CuraGen's expectation that it will incur operating losses in the near future, the early stage of development of CuraGen's products and technologies, uncertainties related to preclinical and clinical testing and trials, uncertainties and adverse results relating to CuraGen's ability to obtain regulatory approval for its products in development, uncertainties surrounding the availability of additional funding, CuraGen's reliance on research collaborations and strategic alliances, the actions of competitors, the development of competing technologies, CuraGen's ability to protect its patents and proprietary rights, patent infringement actions and uncertainties relating to commercialization rights. Please refer to our Annual Report on Form 10-K for the fiscal year ended December 31, 2001 for a description of these risks. We disclaim any intention or obligation to update or revise any forward-looking statements, whether as a result of new information, future events, or otherwise.

SOURCE CuraGen Corporation

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